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Bipolar Genetics

Research Update

The Shifting Genetic Landscape of Bipolar Disorder

By Francis J. McMahon, M.D., Chief, Genetics Basis of Mood & Anxiety Disorders

In the last year or two, there has been rapid progress in understanding the genetic underpinnings of the common mental illnesses, such a bipolar disorder. How rapid? Imagine a distant landscape out near the horizon. As we draw closer, some things turn out to be illusions, while others, previously invisible, draw more sharply into view. The pace at which the landscape is now shifting may give us the best feel for how rapidly the research is progressing. New treatments or diagnostic tools may be just over the horizon, or may be much further off, but one thing is clear: We are moving forward faster than ever before.

The rapid pace of progress is driven in large part by enormous advances in genetic technology. Scientists now possess genetic tools of unprecedented power, allowing us to survey the entire human genome in vast numbers of people in a matter of hours – unthinkable a decade ago. These new technologies first made it possible to test common variation spanning all chromosomes, both within genes and between them, in so-called genome-wide association studies (GWAS).

Our group published the first GWAS of bipolar disorder in the Spring of 2008, followed closely by groups in the United Kingdom and Boston. As of Spring 2010, four GWAS have appeared

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Francis J. McMahon, M.D.

NIMH Genetics Researchers Spearheading an International Effort to Study the Genetic Basis of Response to Lithium in Bipolar Disorders

By Thomas Schulze, M.D.

For more than half a decade, lithium, a naturally occurring salt, has been successfully used to treat bipolar disorder. Worldwide, it is considered the first-line mood stabilizer. Apart from its proven anti-manic and preventive effects, considerable evidence also suggests an antisuicide effect in mood disorders. Lithium is also effectively used along with antidepressant drugs in the treatment of refractory major depressive episodes and to help prevent relapses in major depression.

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NIMH National Institute of Mental Health

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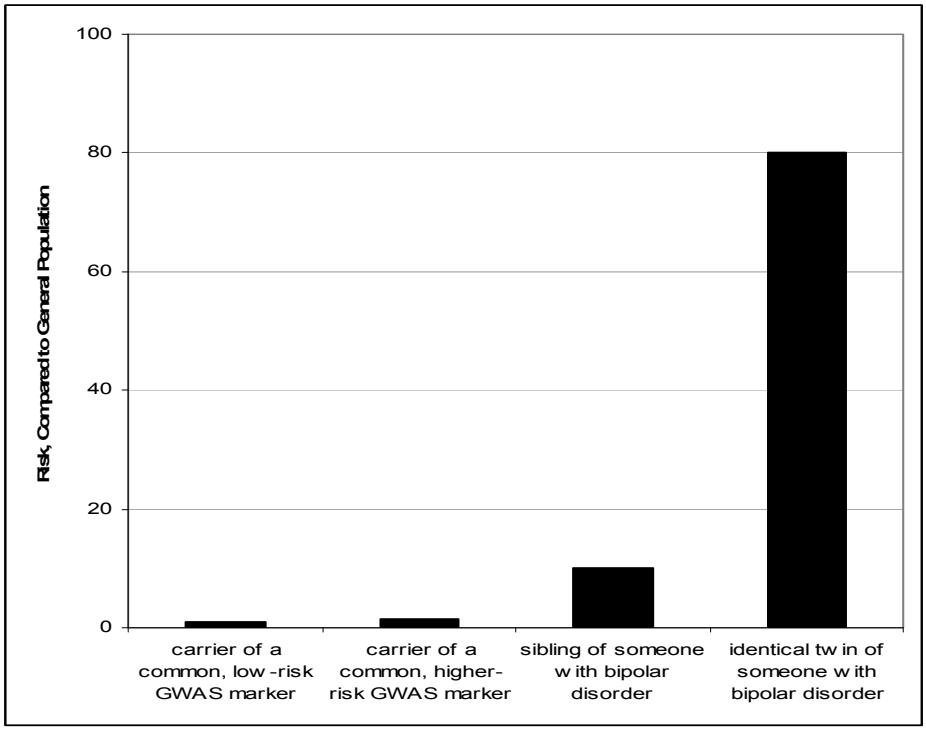
in bipolar disorder and major depression, along with several studies that combine the results of other published studies in so-called 'meta-analyses'. At least one gene seems to influence risk for both major depression and bipolar disorder, while others seem to contribute to both bipolar disorder and schizophrenia. These studies, along with others published in schizophrenia, have provided something we never had before in psychiatric genetics: robust, reproducible connections between genetic markers and psychiatric illness.

But the news is not all good. The several GWAS published to date, with sample sizes now exceeding 10,000, have so far failed to find any genetic markers that have much of an impact on an individual's risk for bipolar disorder. Individual markers seem to account for less than 1% of the risk for bipolar disorder [see figure]. Even if we consider all of the common genetic markers together, they account for something on the order of 3% of the risk. We already know from twin studies that at least 60% of the risk for bipolar disorder is genetic. So what is going on?

Our best guess right now is that the genetic risk for bipolar disorder has simply not been captured by the GWAS method. There may be many genes each of very small effect that combine by the dozens to determine risk. There may also be rare forms of genetic variation [sometimes called 'mutations'] that are seen in only a few individuals or families but which when present confer a high risk for illness. Such mutations would be largely invisible in a GWAS, but might be found by large-scale sequencing studies that aim to determine the exact spelling of an individual's entire DNA makeup. Several such studies are now underway. A study we are leading here at NIMH aims to find rare mutations that might help explain bipolar disorder that occurs from generation to generation in large families.



It may not be easy to see what the future holds. Right now, all we can say for sure is that the genetic landscape of bipolar disorder is shifting rapidly. The more we learn, the closer we will move toward the ultimate goal of better diagnosis and treatment for this often devastating illness.

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In contrast to many psychiatric drugs, lithium has outlasted various pharmacotherapeutic "fashions", and remains an indispensable element in contemporary psychopharmacology.

Nevertheless, we still do not know much about how lithium actually works. Several mechanisms have been suggested such as key roles in cell signaling pathways, effects similar to the ones of classical antidepressants, or neurogenesis (i.e. promoting the formation of new neurons or syanpses) among others. Pharmacogenetics (Pgx), the investigation of genetic factors underlying an individual's reaction and response to a medication, is thought to be an important and promising avenue to learn more about how a drug actually works. Pgx could eventually lead to a more individualized therapy, which takes into account a patient's individual response profile to a given medication (also known as personalized medicine).

Whereas several large-scale pharmacogenetic studies have been performed in major depression (see our previous work within the STAR*D consortium), yielding intriguing results on predictors of response and adverse events, there is a lack of pharmacogenetic studies in bipolar disorder, in particular as regards lithium, the most widely used mood stabilizer of all times.

ConLi+Gen

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International Study on Lithium Response, continued from page 1

To change this, our group has initiated the largest initial consortium to study the genetics of lithium response. Led by Dr. Thomas G. Schulze, Assistant Director of Clinical Research of our Unit, we have teamed up with the *International Group for the Study of Lithium-treated Patients* (www.IGSLi.org) and several other leading lithium research groups across the globe and created the world's largest consortium aimed at deciphering the genetic basis of response to lithium in bipolar disorder.

On May 6th, 2008, researchers from North America and Europe met at the NIMH and inaugurated the *Consortium on Lithium Genetics (short: ConLiGen; www.conligen.org)*. Since then, many more groups have joined *ConLiGen*. Member groups include researchers from several centers in the USA, Canada, Germany, Poland, Italy, Japan, and Taiwan. These groups have committed to contribute study samples of patients suffering from bipolar disorder and having taken lithium at at least one point during the course of their illness. Our group is charged with joining these various samples and preparing them for genetic analyses. This effort has been approved by the ethics committees and institutional review boards of all centers involved; it is in line with all applicable regulations of privacy and data protection.

So far, the combined *ConLiGen* sample comprises around 1,400 individuals suffering from bipolar disorder. An estimated further 1,000 samples will become available within two years. In addition to combining all available clinical data, we are currently preparing the DNA of the individuals included in *ConLiGen* in order to perform a genome-wide association study (GWAS). Here, we screen the whole genome of an individual for genetic variation that might determine a patient's response to lithium medication. We are defining response to lithium using an internationally established scale, according to which patients can be characterized into responders, partial responders, and non-responders. Typically, around 30% of patients will fall into the first category. While they may not be completely free of some mood symptoms, they will typically show an absence of major manic or depressive episodes since the inception of the lithium treatment. Partial responders are those patients, for whom lithium medication has substantially decreased the frequency of manias or depressions or their severity. Non-responders are characterized by a complete absence of any benefit of lithium. Within the *ConLiGen* consortium, response to lithium is rated based on a thorough chart review and a personal, structured interview with the patient. We are expecting the first results of our GWAS in the *ConLiGen* sample by the end of 2010 or early 2011.

We are happy to announce that we have been able to establish an Advisory Board comprising international experts in the field of mood disorders research, among them a Nobel laureate and members of the National Academy of Sciences. The Advisory Board will offer *ConLiGen* an outside perspective as well as guidance on broad scientific directions, serve as a liaison to non-academic communities such as funding institutions, or industry, and finally, act as one of *ConLiGen*'s publicly visible faces. Currently, the following researchers are members of the Advisory Board (in alphabetical order): Robert H. Belmaker (Division of Psychiatry, Ben Gurion University of the Negev, Beersheva, Israel), Gian Luigi Gessa (Department of Neuroscience "B.B. Brodie", University of Cagliari, Italy), Paul Greengard (Laboratory of Molecular and Cellular Neuroscience, Rockefeller University, New York, NY, USA), Kay R. Jamison (Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA), Richard S. Jope (Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA), Husseini K. Manji (CNS & Pain, Johnson and Johnson Pharmaceutical Research and Development, Titusville, NJ, USA), and Leon E. Rosenberg (Department of Molecular Biology, Princeton University, Princeton, NJ).

ConLiGen has been presented to the scientific community at major national and international conferences such as the meeting of the American College of Neuropsychopharmacology (ACNP; Scottsdale, AZ, 2008, and Hollywood, FL, 2009), the meeting of the Society of Biological Psychiatry (SOBP; Vancouver, BC, Canada, 2009), the World Congress of Psychiatric Genetics (WCPG; Osaka, Japan, 2008), and the congress of the World Federation of Societies of Biological Psychiatry (WFSBP, Paris, France, 2009).

60 years after the discovery of lithium as a therapeutic agent for bipolar disorder by the Australian psychiatrist John F. Cade, lithium remains the world's number one mood stabilizer. Moreover, potential therapeutic effects of lithium have been reported for neurodegenerative disorders such as Alzheimer's dementia. *ConLiGen* will contribute to a better understanding of the genetic mechanisms behind lithium's mode of action.

Thomas Schulze, M.D.

Genetics and Neuroimaging: A New Way to Understand How Genes Work in the Biology of the Human Brain

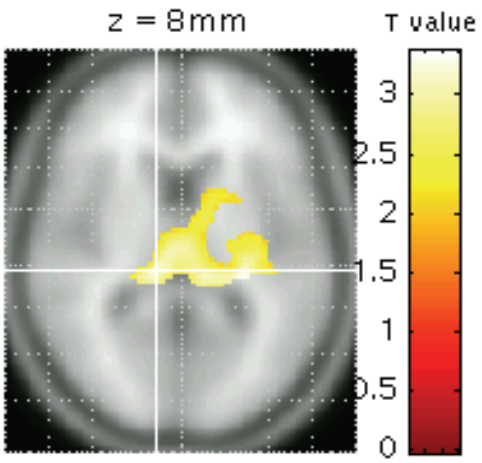
By Gonzalo Laje, MD, MHSc

For over two decades we have been working on finding genetic markers to predict mental illness such as bipolar disorder and depression. The search for these markers has two main goals: 1. better diagnosis for individuals suffering from a mental illness, and 2. increased understanding of the biological processes behind these illnesses, so that better treatments can be developed. Genetic markers usually reflect differences in the sequence, or spelling, of the DNA that are more common in people with the illness than in those without the illness. However, genetic markers alone rarely provide much information about biology. Neuroimaging is one promising way to move from genes to biology.

Neuroimaging, the ability to take a "picture" of the brain in a living person, is a rapidly evolving science. There are several different methods that can obtain very detailed images of the brain through the use of low-doses of radiation (such as CT scans or PET scans) and others that obtain images using magnets (MRI and MRS scans). We can also use these methods to determine the concentration of certain chemicals, such as proteins, in specific areas of the brain. We can ask how changes in the DNA sequence have an impact on these chemicals. Answers to questions like these may ultimately help us better understand the biology of mental illness.

Dr. Wayne Drevets [now at the University of Tulsa], has perfected a PET scan method that measures the amount of a protein called the serotonin transporter in the brain. The serotonin transporter is the main target for the selective serotonin reuptake inhibitor [SSRI] antidepressant medicines such as fluoxetine, sertraline, and citalopram. We wondered whether the amount of serotonin transporter in the brain might have something to do with who responds best to SSRI's.

In recent years we have identified genetic makers in two genes that are related to how depressed patients will respond to antidepressant medication. Both of these genes encode proteins that are at the receiving end of major chemical messenger systems in the brain: HTR2A, which encodes the serotonin 2A receptor, and GRIK4, which encodes a key part of a glutamate receptor. In collaboration with Dr. Drevets, we found that the same genetic markers that were associated with antidepressant response were also associated with the amount of serotonin transporter present in key areas of the brain. These findings are interesting because they form a link between the main target of SSRI's, the serotonin transporter, and genetic markers in HTR2A and GRIK4 that are more common in people whose depression responds to SSRI's. These findings provide a potential new explanation of how genes interact with medication in the treatment of depression. We are currently conducting additional experiments to further understand this interaction. We are particularly interested in the chemical messenger glutamate, which other research also suggests plays an important role in antidepressant response. We'll keep you posted!



Brain image showing the area with the association between the serotonin transporter and markers implicated in antidepressant response.

Laje, G. et al. Genetic variation in HTR2A influences serotonin transporter binding potential as measured using PET and [11C]DASB. Int J Neuropsychopharmacol. 2010 Jul;13(6):715-24.

Gonzalo Laje, M.D.

Web Sites of Interest

NIMH Genetic Basis of Mood and Anxiety Disorders Unit - http://mapgenetics.nimh.nih.gov/
NIMH Bipolar Genetics Initiative - http://www.bipolargenes.org/
NIMH Neurosciences research - http://neuroscience.nih.gov/

About bipolar illness and clinical studies:

National Institute of Mental Health - http://www.nimh.nih.gov/
NIMH Publication Order Form - http://infocenter.nimh.nih.gov/
NIH-sponsored Clinical Trials- http://www.nimh.nih.gov/health/trials/
Other Clinical Trials - http://www.clinicaltrials.gov/

Who's Who in Bipolar Disorder Genetics at NIMH

Francis J. McMahon, Chief. Dr. McMahon graduated from the University of Pennsylvania in 1982, with a B.A. in Biology. After a year in Germany as a Rotary Scholar, he enrolled in The Johns Hopkins University School of Medicine, where he received his M.D. in 1987. He stayed on at Hopkins to complete a medical internship, a residency in adult psychiatry, and a post-doctoral fellowship in genetics before joining the faculty in 1993. In 1998, he became Associate Professor of Psychiatry at the University of Chicago, where he also served as medical director of the Electroconvulsive Therapy clinic. In 2002, he moved to the National Institute of Mental Health to establish a new Genetics Unit within the Mood and Anxiety Disorders Program (MAP) Dr. McMahon has authored over 100 scientific publications. He is the recipient of several honors and awards. In 2008, he received a NIH Director's Award. He serves as a scientific advisor for the National Tourette Syndrome Association, the American Foundation for Suicide Prevention, and the Rutgers Cell and DNA Repository. He serves on the editorial boards of the International Review of Psychiatry, World Psychiatry Journal, and Biological Psychiatry. He is a member of the American College of Neuropsychopharmacology, the American Psychopathological Association, and the International Society of Psychiatric Genetics, where he is an elected member of the Board of Directors.

Sevilla Detera-Wadleigh, Staff Scientist. Dr. Wadleigh's research interest centers on defining the genetics of bipolar disorder with over 100 peer-reviewed publications and book chapters. She has conducted whole genome linkage scans and allelic association of candidate genes in mood disorders, and has been involved in spearheading and organizing the first comprehensive meta analysis of linkage scans in bipolar disorder. With the emergence of new candidate risk genes for mood disorder from genome-wide association studies, she has trained a new focus on functional genomics – investigating the global effect on signaling pathways and interaction networks following disruption of risk gene expression. She is also examining pathways and functional clusters perturbed by mood stabilizers through the analysis molecular networks, extending her previous work on the cloning of the gene for myoinositol monophosphatase 2, an important target of lithium. She is a member of the editorial board of two psychiatry journals.

Thomas Schulze, Assistant Director. Dr. Thomas G. Schulze studied medicine in Germany, the USA, and Catalonia. He trained as a psychiatrist and held positions in Germany (Bonn, Mannheim) and the USA (Chicago, IL; Bethesda, MD; Baltimore, MD). Since 12/2007, he has been serving as the Assistant Director of Clinical Research within the Unit on the Genetic Basis of Mood and Anxiety Disorders of the NIMH. He also holds a position of Adjunct Assistant Professor with the Department of Psychiatry and Behavioral Sciences of Johns Hopkins University.
Dr. Schulze's research focuses on genotype-phenotype relationship in bipolar disorder and related psychiatric disorders and on the development of novel statistical tools to perform such studies in a systematic fashion.

Dr. Schulze has authored more than 100 papers in leading journals. His awards include grants from German and US funding agencies. He is the 2006 recipient of the *Robins-Guze-Award* of the American Psychopathological Association (APPA), the 2006 recipient of the *Theodore-Reich-Award* of the International Society of Psychiatric Genetics (ISPG), the 2007 recipient of the *Future Award* of the German Society of Bipolar Disorders, and the 2009 recipient of the *Hans-Jörg-Weitbrecht Award for Clinical Neuroscience* of the German Psychiatric Association. He is furthermore a member of the Junior Academy of Young Scholars and Scientists of the Academy of Sciences at the University of Heidelberg (Germany), an Associate Member of the American College of Neuropsychopharmacology (ACNP), member of the Board of Directors of the ISPG.

Layla Kassem, Psychologist. Dr. Kassem completed her doctorate in clinical psychology in 1993. She completed her postdoctoral training in Boston and Chicago. She is currently working on two projects. The first is at NIMH/NIH, at the Genetics of Mood and Anxiety Disorders Section, and the second is at the University of Chicago in the Committee on Human Development. Her interests include genetics of chronic psychiatric disorders and cultural issues in diagnosis and treatment. Her main responsibilities at NIMH include family interviews, and the analysis of clinical data. Her work at University of Chicago includes cross-cultural research on psychiatric disorders and their phenotypes as well as the interface between traditional healers and trained psychotherapists, and

Genetic Basis of Mood and Anxiety Disorders Unit: Standing from the left (back row): Girma Hawariat, Jens Wendland, Nirmala Akula, Francis McMahon, Jo Steele, Kecia Dickerson, Diane Kazuba, (front row): Gonzalo Laje, Lisa Pfeifer, Sevilla Detera-Wadleigh, Sara Richardson, Elise Bui, Carol Markey, Xueying Jiang, and Xinmin Liu.

the evolution of the field of psychiatry in Lebanon and Egypt..

Nirmala Akula, Bioinformatician. Dr. Akula received a masters in biotechnology from India in 1997. She then came to USA and earned a masters in biology from Illinois Institute of Technology in 2001 and a masters in computer science from University of Chicago in 2002. She graduated with a PhD in bioinformatics from George Mason University in January, 2010. She has been working on the genetics of major mood disorders since 2000. She conducts genome-wide association studies (GWAS) and data analysis. She recently developed a software tool, Network Interface Miner for Multigenic Interactions (NIMMI) that identifies susceptible networks/pathways using GWAS data.

Jo Steele, Data Manager. Ms. Steele has been involved with the bipolar genetics project for about 15 years, primarily managing the large quantities of data that are generated. For the last 8 years she has been at NIMH, where she prepares the laboratory and clinical data for analysis. Previously, she worked with Dr. McMahon and others at Johns Hopkins University, in Baltimore. She has a B. Eng (Hons) in Electronics from Southampton University, in the United Kingdom.

Winston R. Corona, Biologist. Mr. Corona was born in Chile and obtained a degree in engineering in 1981 from the University of Chile in Santiago. After coming to the United States he obtained a B.S. degree in environmental sciences and marine biology in 1995 from the University of the District of Columbia, and in 2005 he obtained his M.S. in biochemistry and molecular biology from Georgetown University in Washington, DC. His interest in research involving pure sciences began in 1984 after traveling around the Atacama Desert in the north of Chile. This brought him to NIH to work as a special volunteer in 1999. He is co-author of five publications.

Diane Kazuba, Site Coordinator. Ms. Kazuba received her BS degree at the University of Maryland in Psychology and Social Work. She began working in the Clinical Genetics Branch at the National Institute of Mental Health (NIMH) in 1986. There she was mainly in-

Who's Who in Bipolar Disorder Genetics at NIMH

volved with genetic studies of siblings with bipolar disorder and schizophrenia. In June of 1998 she transferred to the Adult Obsessive-Compulsive Disorder (OCD) research unit at NIMH, where she remains involved in family studies of OCD and bipolar disorder. She is responsible for recruitment and enrollment of study volunteers and conducts clinical interviews with patients and their family members.

Gonzalo Laje, Associate Clinical Investigator. He received his MD from the University of Buenos Aires in Argentina in 1995 and a Master of Health Sciences in Clinical Research from Duke University. He completed his training in general psychiatry at New York University/Bellevue Hospital in New York City, and trained in child and adolescent psychiatry through the combined program NIMH/ Children's National Medical Center in Washington, DC. Dr. Laje has been the recipient of multiple awards in the fields of psychiatry and child psychiatry. He joined the Genetic Basis of Mood and Anxiety Disorders program in 2005. His research interests include pharmacogenetics of mood and anxiety disorders and psychiatric aspects of genetic disorders.

Jens R. Wendland, Fellow. Dr. Wendland received his M.D. degree from the University of Wurzburg, Germany, in 2003. He completed an internship in adult psychiatry and joined the NIMH in 2004. His initial work at the NIMH was focused on the genetics of obsessive-compulsive disorder and of the serotonin transporter. Since joining the Unit on the Genetic Basis of Mood and Anxiety Disorders in 2009, Dr. Wendland has been primarily involved in bipolar genetics studies and analyses of the brain transcriptome.

David Chen, MD, Clinical Research Fellow, joined the lab in July 2009. He is an ABPN Certified Psychiatrist specializing in Child and Adolescent Psychiatry. Having graduated from University of Rochester School of Medicine, he completed his adult psychiatry residency at University of Maryland/Sheppard Pratt as chief resident in 2007. Thereafter he completed his Child and Adolescent Psychiatry Fellowship at Children's National Medical Center. In July 2009, Dr. Chen was awarded the 2009 American Academy of Child and Adolescent Psychiatry Lilly Pilot Research Award. His project focuses on pediatric onset bipolar disorder.

Xueying Jiang, Biologist. Ms Jiang received her M.D. from XinJiang Medical School in China in 1988, and her PH.D. in pharmacology at Chinese Academy of Medical sciences& Peking Union Medical College Peking in 1994. She completed her postdoctoral training at Department of Pharmacology, University of Maryland. From 2001 to 2006, she worked as a research assistant professor in the Department of Neurology, Uniformed Services University of the Health Sciences (USUHS), and participated in several research projects conducted by both National Institute on Alcohol Abuse and Alcoholism (NIAAA) and USUHS. Then she worked as a research scientist at the NIAAA/ NIH, Section of Molecular Neurogenetics in Laboratory of Neurogenetics for 2 years. She joined the National Institute of Mental Health's Unit on the Genetic Basis of Mood and Anxiety disorders as a biologist at the end of 2008.

Carol Markey, Technician. Ms. Markey graduated from the University of Michigan. She joined the NIMH intramural program in 1993. Prior to that she worked in a biochemistry laboratory on developing procedures to measure damage to neuronal DNA and the progression of Parkinson's and Alzheimer's diseases. She has been working on genetic disorders since 1995. From 1995 to 1998 she was part of the Unit on Molecular Clinical Investigation in the Clinical Neurogenetic Branch. During that period she was involved in a schizophrenia genetic study. In 1998, she joined the NIMH Laboratory of Genetics. She participated in genome-wide genotyping studies of complex trait diseases including breast cancer, melanoma, prostate cancer, and schizophrenia. She also worked on the compilation of a G protein-coupled receptor library for the Mammalian Gene Collection. She joined the Genetic Basis of Mood and Anxiety Disorders lab in July of 2005.

Questions, Comments?
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Girma W. Hawariat, Statistician in Medicine. Dr. Hawariat received his BS in Biology from Haile Selassie University, Ethiopia and MS and PhD degrees in quantitative genetics from Texas A&M University with a fellowship of The United Nations. He did his postdoctoral training in quantitative genetics at The University of Wisconsin-Madison and a second postdoctoral training in molecular/cellular biology in The College of Medicine of The State University of New York at Syracuse. He served as a research scientist in molecular/cellular biology of cancer at The George Washington University Medical Center (Children's Hospital) and as an Assistant Professor in the same area in The College of Medicine of The Uniformed Services University of The Health Sciences. Dr. Hawariat has authored and co-authored 16 papers.

Lisa Pfeifer, Graduate Student. Ms. Pfeifer received her B.A. degree in Biological Basis of Behavior from the University of Pennsylvania in 1998. While at Penn, she also helped conduct clinical trials in the Department of Neurology of the Hospital of the University of Pennsylvania. Ms. Pfeifer also has a Master of Applied Anthropology (2001), Master of Science in Biology (2005) and a PhD in Biology (2010), all from the University of Maryland. As a National Science Foundation IGERT Doctoral Fellow, Ms. Pfeifer studied variation in two hormone receptor genes in worldwide human populations and other primates. She combines training in multiple areas, including neuroscience, anthropology, and population genetics, to study genes that influence social behavior. Ms. Pfeifer's other research interests include the role of rare variants in human disease, gene/environment interactions, and how early-life events affect susceptibility to mood and anxiety disorders.

Elise Bui, Pre-doctoral Fellow. Ms. Bui has been with the Genetic Basis of Mood and Anxiety Disorders program since August 2009. She is involved with both the clinical and labwork aspects of the program, which includes interviewing participants, handling clinical data, managing DNA samples, and genotyping. Elise graduated with distinction from the University of Virginia with a B.S. in Biology and a B.A. in Psychology. She plans to pursue further education in psychology after her time at the NIMH.

Reena Clements, Summer Intern. Ms. Clements has joined the NIMH for the summer in order to broaden her experience in neurogenetic research. She is working under Dr. Detera-Wadleigh, studying genes which are associated with bipolar disorder and schizophrenia. Her previous research experience includes work in neuromuscular disorders. Ms. Clements is a member of the class of 2013 at Boston University and is pursuing a BA in Biochemistry and Molecular Biology, and Neuroscience.

Medgine Mesidor, Volunteer. Miss Mesidor was born in Haiti. She obtained her Certified Nursing Assistant license in 2003. Upon completion of a medical career program, she volunteered at Bethesda Naval hospital and Randolph Hill nursing home. She received her Bachelor's of Science in biology at Clark Atlanta University in 2008. She is currently working towards a masters degree in pharmacology at Howard University. While volunteering at NIMH, her objective is to increase her knowledge base in clinical studies as well as the applicability of laboratory research.